

**Amendments to the specification:**

All of the specification amendments are content taken from the related Provisional Application No. 60/319,436 and had been pasted here. Exact pasting had been executed, therefore to the applicant's best knowledge the information below does not contains new matter. No parts had been deleted because of any particular content, and the applicant is aware that the provisional application had been made public.

Please add the following new paragraphs before the paragraph on page 18 that begins with "whereas particular embodiments of this invention",

For the PTO's convenience we have added the page numbers – inserted into tables -of where the pasting came from.

As per the phone interview with the PTO grammatical changes were allowed – we have clearly marked that by strikethrough and [in marked squared parenthesis the added correction]. Additionally we have drawn attention to that changes in the box where the note appears that from what page number the pasting came from.

**Amendments to the specification (pasted from the provisional application):**

PTO page 31 of 88: 0226 line 5 on – till page 32 0229 line 2; (=my copy with font 14 [also enclosed] it is page 43 2<sup>nd</sup> paragraph line 5-23.):

As in all treatment, the final decision is (always) up to the patient and the treating clinician. Offering to our patients more than one options that include the combination use of psychotropic medications can show many advantages. With this we are involving them in the decision-making, but we are supposed to discuss with them the risks/benefits, side effects of the medications, and available alternatives anyway.

If the patient opts to take only one medication, an antidepressant, let's work with him or her. But if the patient (as usual) is 'tormented' by the depression or depression and anxiety, or has a suicidal ideation, hopelessness, or (after we educate them) expects/wishes an "immediate" improvement [although – like most depressed – still maintaining his/her 'basic beliefs' that "nothing would help anyway"], we should put more weight on the use of medication combination (preferably by adding an atypical neuroleptic or a "dopamine system stabilizer").

In psychiatry we are not afraid of prescribing more than one medications to our patients, and the treatment of depression should not be an exception.

The treatment of depression can be started right away with more than just one medication, the antidepressant.

PTO page 32 0229 line 20 – page 33 line 23: (=my copy font 14 page 44 2<sup>nd</sup> paragraph line 6-32.):

Predicting which patients will commit suicide is an impossible task, and there are no models of suicide risk assessment that had been empirically tested for reliability and validity. (Simon, R.I., 2002.) It is often difficult for the clinicians to assess the risk of suicide systematically, due to the large volume of the patients, and due to the limited time and resources. The information being available is often limited. There is a continuum in the risk assessment from only asking the patients if they are suicidal, to performing formal systematic suicide risk assessment. It had been admitted even in academic publications that the former is much more common. (Simon, R.I., 2002.) Unfortunately, according to Simon, the "no harm contract" is unreliable, and short hospital length of stay, rapid patient turnover,

brief outpatient and partial hospitalization visits, and the split treatment in managed care setting, results in difficulties and that the suicide risk factors are usually not recognized by the clinicians. (Simon, R.I., 2002.) Only the sickest patients are admitted to inpatient psychiatric units, (Simon, R.I., 2002), and the average length of stay (median) for depression/mood disorder can be as little in some (multi-county US) geographical areas as six days. (Mode: 4 days). The length of stay for patients whose medication need to be adjusted may actually be even less, as patients requiring ECT take off from the average hospital days from the former group. (Depression and other mood disorders in Southwestern Pennsylvania). The assessment of suicide is further complicated by the fact that approximately 25% of patients at suicide risk do not admit to being suicidal. (However, in most cases they had communicated suicidal ideation or intent to family members.) (Fawcett cit#18. < also referenced in: Simon, R.I., 2002). Patients, who deny suicide risk, usually do not meet Managed Care criteria for hospitalization.

PTO page 34 of 88: 0232- till page 35 till 0235; (=my copy font 14 page 45 4<sup>th</sup> paragraph line 1- page 46 line 18):

We have to balance the risk / benefit of our intervention both for the individual patient and for the group of patients we are treating. This had been customary for long, in the medical practice. A good example for this is of how we were treating appendicitis. If the patient showed some typical symptoms that he or she *might* have appendicitis (specifically if the WBC was also elevated), then the surgeon was operating on. The surgeon had rather operated on healthy people for whom it turned out on the operating table that they did not had an infected appendix, (taking out the appendix anyway), then wait until it became obvious that the appendix had perforated. This is quite a standard procedure that surgeons followed. The risk of dying from the operation (without an infected appendix) was far less compared to waiting and having the (high) risk of death from operating late with a perforated appendix. The clinicians have a responsibility of not only weighting the risk of the individual but also the risk of a group.

We are following similar procedures and we give thiamin routinely for everybody in the emergency room before giving IV glucose, (therefore preventing Korsakov's syndrome in alcoholics). We are routinely testing for drug screen in the ER (and the patient gets charged for the cost); even when the patient says that he or she is absolutely not taking any illicit drugs. This is a standard procedure and good clinical practice. The risk of being operated on or getting a blood or urine drug screen is not the same. Nevertheless, we take into account the risk/benefit for a group not just for an individual. So why are we not more vigorous in preventing suicide? We are not saying that we should blindfoldedly prescribe a combination of psychotropic medication for every depressed person against their will, but to discuss the *risks / benefits* and *alternatives* with the patients as we mentioned it above. It is fortunate, that in this case, with the medication combination we are not only targeting the reduction of suicide (for the individual and for the group as a whole) but other benefits as well, such as a more rapid resolution of the depressive symptoms, the reduction of anxiety, and even a higher response rate (in %) to the treatment. (One could speculate that if using the SSRI-atypical neuroleptic combination would increase the response rate of treatment-resistant depression, then the percentage rate for improvement would be also higher if given for everybody who is clinically depressed, that is without separating the 'responders' from the 'non-responders'. This speculation is probably correct, but by itself would not substantiate the added risk using the neuroleptics. With this rationale, the two step strategy would seem still to be the logical step, to treat the depressed patients with antidepressants first, and reserve other strategies for the treatment-resistant group only. In the argument to consider, or start using the combination treatment right away in all those who are clinically depressed, it is the decrease of suicide rate that is the paramount important factor. The other added benefits from the medication combination

like the “immediate” response, the decrease of anxiety, or a higher response rate as for the whole group are only secondary.

PTO page 22 of 88: 0200 – till page 23 0203; (=my copy font 14 page 34 3<sup>rd</sup> paragraph line 1- page 35 end of 3<sup>rd</sup> paragraph.):

It had been noted that in assessing suicide the focus should be on the characteristics of those who commit suicide rather than on the characteristics of patients with suicidal ideation. (Forster P., 1994.) The same article also notes that major depression is associated with the largest number of completed suicide and half or more of all who commit suicide qualify for this diagnosis. About 15% to 20% of all patients with serious affective disorder will kill themselves. (Forster P., 1994.).

On the other hand 8% of borderline personality disorder (BPD) patients will commit suicide. (Forster P., 1994. – cit#21.). BPD is a separate diagnostic category from major depressive disorder and not even listed under the mood disorder category (See DSM-IV-TR.). It is also known that in treating borderline personality disorder (BPD), we are using “all of the available psychotropic medications, and combinations of them”. (See also Gabard’s video 9/11/1992, – and published by APA in 1995, Markovitz, P. J. et al. 1991, **versus patent # 5,589,512 on BPD** filed January 1994,). It is true, depression is only one of the comorbid conditions associated with BPD, some others being rejection sensitivity and cognitive distortions to the extent of “mini psychosis” (See also Gabard’s video 9/11/1992, – and published by APA 1995). (For diagnostic criteria please refer to DSM-IV TR.) Our point is that with this disorder we were not afraid of using the combination of antidepressants with antipsychotic medications or even adding a mood stabilizer. Yet in major depressive disorder; in serious affective disorder *with 2-2 ½ times more risk for committed suicide*, we continue to refrain from using or even trying this combination. In BPD at times we are even using clozapine (Clozaril) despite for its high risk for agranulocytosis and despite that it had been prohibitively costly, due to the need of weekly or biweekly blood draws (Frankenburg, et al. 1993). We are not recommending Clozaril to treat major depression or other depressive disorders, (see also patent#: 4,310,524 Apr. 1980, on TCA and  **$\alpha$ -adrenergic receptor blocking agent: clozapine, to achieve rapid onset antidepressant activity. Please note, the antidepressant is TCA, not SSRI, or not of the new generation.**), when other much safer (and cheaper) atypical antipsychotic medications are now on the market. However, we do advocate taking a closer look, and considering using the “new generation atypical neuroleptics” or the even newer “dopamine system stabilizers” together with the antidepressants.

What is deceptive at the first look is, that patients with BPD may show more frequent suicidal gestures and may struggle with almost constant suicidal ideation, but the fact remains that the risk of committing suicide is still 2-2 ½ times more in people with serious affective disorder than in BPD. [For the statistics of suicide risk, please see: (Forster P., 1994.)]

For us in the medical profession it would not be fair to continue hiding under the excuses of the added risk of the potential side effects of the antipsychotic medications, specifically with the availability of some of the safer atypical antipsychotics.

at PTO page 35 of 88: 0236 line 4 – page 37 till 0241; (=my copy font 14 page 46 3<sup>rd</sup> paragraph line 1- till page 48 end of 1<sup>st</sup> paragraph.):

One of the major concern about to use a neuroleptics had been their potential side effects. Although even with the traditional antipsychotics the development of neuroleptic malignant syndrome (with fever,

rigidity, and increase in creatine phosphokinase - CPK) had been rare, but this syndrome is potentially lethal. Now that the psychiatrists are more aware of that syndrome they may be able to intervene and start treating it early with better outcomes. In addition and more importantly, the development of neuroleptic malignant syndrome (NMS) may be diminished with atypical antipsychotics. (Caroff, S. N. et al. 2002.).

Another concerning side effect is tardive dyskinesia that has a prevalence among individuals treated with traditional antipsychotics that range from 10% to 15% in young patients, and 12% to 25% in chronic patients. It is has been estimated that up to 90 percent of the cases of tardive dyskinesia goes unrecognized even in academic residency training inpatient units. (Rotrosen, J., et al. 1995.). Vitamin E might prevent or reverse this side effect and have prophylactic or therapeutic benefits. (Rotrosen, J., et al: 1995.).

However, the atypical antipsychotic drugs are associated with reduced potential for inducing extrapyramidal symptoms and other movement disorders. Atypical antipsychotics have reduced liability for inducing tardive dyskinesia and show antidyskinetic properties in patients with existing TD. With quetiapine it is reported that the risk of TD was similar to olanzapine and significantly less than haloperidol in all age groups. With olanzapine the annual risk of TD is estimated about 1/12<sup>th</sup> of the risk associated with haloperidol. One year risk of TD of all patients was calculated to be 0.52% with olanzapine and 7.45% with traditional haloperidol. The annual risk of TD with risperidone is 1/6 of the risk of haloperidol or 1/6<sup>th</sup> to 1/10<sup>th</sup> of the conventional drugs. (Caroff, S. N. et al: 2002.). The "dopamine system stabilizers" are expected to have even less adverse effects (Krammer, T.A.M., 2002).

Carroff's article also reports that combining data from many studies indicate that the relative risk of drug-induced acute extrapyramidal symptoms or EPS may be expressed in declining order in the following: the typical antipsychotics (high potency > low potency) > atypical antipsychotics (risperidone > ziprasidone >= olanzapine > quetiapine). [See also ref. for the later for EPS being like with placebo.] This article also states that "*There is a fairly consistent and convincing evidence that the atypical antipsychotics have significantly reduced liability for TD and are also effective in suppressing dyskinesia in patients with preexisting TD. In some studies of atypicals the incidence of TD is no greater than the rate of spontaneous dyskinesias among untreated schizophrenic patients.*" (Caroff, S. N. et al: 2002.).

Although written consent for neuroleptics are not required for outpatient setting, many large institutions adapted such a policy. The side effect profile of atypical antipsychotics is so much less, that in a health system that is a part of a major chain of medical and psychiatric / inpatient and outpatient services, a meeting was held, where the issue of abandoning their written consent form for TD/NMS was seriously considered. (Written communication).

PTO page 48 of 88: 0286- till the end of 0288; (=my copy font 14 page 59 4<sup>th</sup> paragraph line 1- till page 60 end of 2<sup>nd</sup> paragraph.):

The issue of how long one should take an antidepressant needs to be discussed with the patient. There are only general guidelines for this. The "rule of thumb" varies by how many times the patient relapsed (possibly also taking into account the family history), the patient's age, and (with the newer safe antidepressants) if the patient wants to risk a relapse. These guidelines are known to the clinicians. Since there are no data on starting the treatment of depression right away with the combination of psychotropic medications, no definitive guidance can be given on how long one should continue to take the neuroleptic. The only data we can rely on comes from treating psychotic depression and from the

sporadic case reports in the treatment of refractory depression. In some of the case reports when either the patient run out of risperidone over the weekend (Kaplan, M. 2000), or when 3 weeks later it was discontinued (O'Connor, M., et al 1998) the patients anxiety or agitation returned. Again these were treatment-resistant depression. The reinstated medication (neuroleptic) came with an immediate relief. For other patients taking risperidone for 2 weeks or 3 months, the discontinuation of the added neuroleptic did not cause deterioration few weeks later (O'Connor, M., et al 1998). Parker, G., et al. (2002) reports that they have treated treatment-resistant non-psychotic depression, and one of their patients presented in a case report improved with the addition of olanzapine, and worsened when it was tapered off. The same response was observed when the atypical antipsychotic was reinstated, or again tapered. Pitchcot, W., et al. (2001) reports that their patient with a long history of treatment-resistant non-psychotic depression improved moderately on venlafaxine but on 5 mg of added olanzapine experienced a marked improvement with a complete remission. However, when olanzapine was stopped due to it's side effect causing weight gain, the patient experienced a new depressive symptom after 4-5 days. Taking the olanzapine again, the patient experienced a dramatic antidepressant response again, maintaining the full remission for 15 months [continuing with the medication combination].

Since TD is still a concern with the atypical neuroleptics, it is fair to say that we should follow a similar 'rule of thumb' then with beztropine: that is to reassess the patient in a few weeks and again in a few months, and attempt to discontinue it if clinically indicated, and the patient is doing well. If symptoms reoccur, that will shift the clinician's decisional balance to reinstate the neuroleptic. For psychotic depression some recommended using the neuroleptic for one year as the depressive relapse is high otherwise. (Keck, P.E. et al. 2000 (a),). Time and experience with this medication combination will teach us more. The patient's history for suicidality, (suicidal risk factors), impulsivity, 'near-paranoia', comorbid disorders (anxiety, alcohol or substance abuse/dependence, personality disorders), or strong cognitive distortions may also guide the clinician toward continuing with the more vigorous treatment of depression with the combination of psychotropic medications.

PTO page 21, 0190 lines 1-4; (=my copy font 14 page 33 lines 4-8.):

*[When we tell to use the medication combination 'right away' obviously we do not mean a single dose of the neuroleptic (like at times it is given for severe agitation in the ER), but a course of treatment, when the medication combination is given for an extended period of time (e.g. 1-2 weeks or longer)].*

PTO page 58, 0336 (after the column [:]) lines 1-4; (=my copy font 14 page 69 Appendix A [of the provisional] lines 1-4.):

In targeting and specifically designing an approach of trying to solve (most/all) of the patient's problems - either pharmacologically and/or with psychotherapy can result in greater success than separate individual strategies alone.

PTO page 23, 0203 – page 31 till 0226; (=my copy font 14 page 35 4<sup>th</sup> paragraph till page 43 lines 1-6.):

[Please also note our remarks for the PTO under Appendix A of the reply to the 1<sup>st</sup> OA – page 78 boxed within the table.] The pasted text appears exactly as we have submitted that to the attorney filing our provisional application. The text was bulleted for heading as appears below.

Let's see some other reasons and other rationales for using the combination of antidepressant antipsychotic medications in clinical depression/major depression (non treatment-resistant major depressive disorder).

- In a retrospective analysis of suicide committers with major depression showed that many of them have received inadequate treatment. (Forster P., 1994.) So if the effectiveness of the antidepressant treatment could be increased in any way, it would be logical that the suicide rates would decrease. Actually, this had already been proven (Rihmer, Z. 2001). Furthermore it had been shown that among the depressed patients who committed suicide many of them actually had psychotic depression that went unrecognized so they were not receiving antipsychotic medications. (Forster P., 1994.) Therefore the adjunctive use of antipsychotic medications could not only enhance the effectiveness of the treatment of depression, but it would also provide a safeguard in case of unrecognized psychotic depression, and therefore – again - prevent suicide. (It had been estimated that a significant proportion, 15% of major depressive episodes fulfill the criteria for psychotic subtype. (Gumnick, J.F. et al. 2000).

In addition, if we were using adjunct antipsychotic medications for the treatment of clinical depression, the overall improvement - as for the group, would also be expected to improve.

Nierenberg had noted that in many cases, the cause of treatment-resistant depression may be an unrecognized psychosis. (Nierenberg, A. A., 1992). (That may explain it again – at least in part – of why did the “treatment-resistant” depression group improve with the addition of an antipsychotic medication.)

- Cognitive distortions like jumping into conclusions without the analysis of the facts; prematurely getting into conclusions, are characteristic for depression. Cognitive therapy specifically addresses this issue by teaching patients of how to recognize and correct these distortions. Others, (Yapko tape) call cognitive distortions as “global thinking”, and report that it is the thinking style of the depressed. It seems however, that there is an overlap between the cognitive distortions; the “mini psychosis” of BPD; and the “full blown psychosis” of psychotics; all of them being out of touch with reality but in different degrees.

We psychiatrists also know that antipsychotics are not particularly effective in chronic delusions with only one delusional idea (monoideatic delusions), nevertheless we are prescribing them despite of its limited usefulness. (The neuroplasticity model for chronic delusion may explain its relative resistance to medications [Spitzer M. 1999]). Now, that we postulate that the atypical antipsychotics may be useful for depression, we may wonder if in fact these medications are - in part - targeting the cognitive distortions that overlap with psychosis. In fact it may be worthwhile considering to reclassify depression as a “thought disorder”, or at least to note that the overlap between depression (mood disorders), and “thought disorders” is not constricted to psychosis or psychotic depression per se. [For those less familiar with the field of psychiatry, disorders like psychosis, schizophrenia, delusional disorders are listed under the category of “thought disorders, and are treated by antipsychotic medications. Depression – with the exception of psychotic depression – was not (and is still not) considered a “thought disorder. However, the particularly strong cognitive distortions in depressed, through the impaired reality testing, in our opinion do overlap with psychosis. In addition, it had been shown, that antipsychotics do show some antidepressive action, so they may be useful in the treatment of depression. All these points to the direction to view depression – at least in part – as a thought disorder]. With this, the use of antipsychotic-antidepressant combination for the treatment of depression gets further supported.

- Cognitive distortions also play a role in anger attacks that 30-40% of depressed patients display. (Koh, K.B. et al. 2002). A significant association between depression and violent behavior in community samples also had been established. (Koh, K.B. et al. 2002). Some reports 28-44% of violent behavior in depressed outpatients. (Hughes, D.H. 1998). Antipsychotics had been used to reduce violence in acute settings, like in ER (Currier, G.W., 2000), and also with psychotic/bipolar patients in long term use. It is also used for 'pathologic aggression' (Collaborative Working Group on Clinical Trial Evaluations 1998 c). Therefore it is questioned again, why don't we use them as adjunct medication in the treatment of depression (major depressive disorder, dysthymia, "double depression"...)?
- It can be speculated that jumping to conclusions without analyzing the facts may lead to impulsivity and may increase the chance for suicide. In fact it is known that impaired reality testing as shown in alcoholism and drug abuse, is associated with significantly increased risk for suicide. Alcohol is associated with 25 to 50% of all suicide and is the second most comorbid factor after depression. (Forster P., 1994.). Therefore addressing cognitive distortions, and/or the source of impulsivity is essential.
- Depressed patients (with their strong cognitive distortions) may not only misperceive information coming from the environment (like miscommunications in their relationships leading to social isolation), but also misperceive stimuli coming from their own body (Szadoczky, E. 2001). In fact increased somatic symptoms are noted in the depressed, (Stahl, S.M. 2002, Kirmayer, L.J. 2001, Kirmayer, L.J., et al. 1993, Szadoczky, E. 2001.), and the majority of the depressed patients present with only physical symptoms to primary care providers (Pincus, H.A. 2001.). This also points out, that part of the problem is with the perceptual disturbance – a symptom, in which just like for delusions it would be logical to use neuroleptics in combination of the antidepressants). [The use of antidepressants in chronic pain and in some somatic problems had been recognized before. (Lynch, M.E., 2001, Bilier, P., et al. 2001, Gruber, A.J., et al. 1996,)].
- It would be important to reassess the role of cognitive distortions in hopelessness and suicide. A study by Fawcet (as referenced in: cit#16 in Forster P., 1994.), confirmed the predictive value of hopelessness in suicide, and that hopelessness is the greatest predictor of suicide risk beyond the first year. However suicide occurs in only 5% of terminally ill patients and their greatest risk factor is untreated depression (Forster P. 1994.). Therefore it is not hopelessness per se, but its perception - that is the cognitive distortion characteristic of depression - that seems to be the most important factor. (For strong perceptual disturbances [e.g. hallucinations,] we had been using antipsychotics.). The adjunctive use of antipsychotics with SSRIs and newer antidepressants in the treatment of depression (major depressive disorders and the like) is again supported by this argument.
- Rumination often seen in the depressed, (e.g. excessive guilt, self-blame, low self-esteem) may overlap with cognitive distortions and also with obsessive-compulsive disorder (OCD). In fact, depression can be viewed that the patients cannot let go of mainly focusing on the negatives. They do ruminate on the negative life events. It is notable, that the adjunct use of antidepressant-antipsychotics was useful in the treatment resistant OCD. (Mohr, N. et al.:2002, Atmaca, M. et al.: 2002). Therefore this medication combination targets another depressive symptom, and substantiates its use for depression, and the decrease of suicide.
- Social withdrawal (and lack of social support) had been also mentioned as a risk factor for suicide. Social withdrawal or lack of social support is found almost half of suicides (Forster P., 1994. [cit#26]). We know that atypical neuroleptics (atypical antipsychotics) improve the "negative symptoms"

including social withdrawal, at least in psychotic patients. (Purdon, S.E. et al. 2001, Berman, I., et al 1999, Keefe, R.S.E., et al. 1999,). Therefore the use of adjunct atypical antipsychotics or “dopamine system stabilizers” in clinical (non-treatment-resistant) depression would be supported by this logic as well.

- Additionally, it is known (separate from all other rational that we list here) that antipsychotic medications, atypical neuroleptics have a positive effect on improving depression in psychotic (schizophrenic) patients. They also reduce hostility and the risk of suicide in this patient population. (Keck, P.E. J. et al. 2000 (b), Collaborative Working Group on Clinical Trial Evaluations, 1998 b,). In fact in an analysis extending to 1 year, in *psychotic patients* the annual suicide attempt rate with atypical antipsychotics showed a 2.3 fold reduction compared to patients receiving haloperidol, an older antipsychotic. (Glazer, W.M. 1998, also referenced in Keck, P.E. J. et al. 2000 (b),).
- We also know that suicidal individuals often find their thoughts constricted to a narrow range of topics and that they tend to constrain their options prematurely. (Forster P., 1994.) In other words this is cognitive impairment and cognitive distortions. Again, the atypical antipsychotic medications had been found to have beneficial effect on cognitive impairment, as measured by psychological testing (at least in psychotic patients). (Purdon, S.E. et al. 2001, Berman, I., et al 1999, Collaborative Working Group on Clinical Trial Evaluations, 1998 a,). That would be an additional support for the adjunctive use of antipsychotic medications with antidepressants in unipolar, non-treatment-resistant depression.
- Some articles also identify the so-called suicidal depressive syndrome (not listed under DSM-IV TR) that patients with major depression at highest risk generally also have feelings of worthlessness, *anxiety*, depressive *delusions* and more *sleep disturbances*. (Forster P., 1994. cit#6). Anxiety itself is a unique and short-term risk factor for suicide, and in patients with major depression, anxiety predicted 93% of suicide within one year of assessment. (Forster P., 1994. cit#5=Fawset). Patients at highest risk for suicide are those with more severe anxiety combined to depression. (Forster P., 1994. cit#17). Therefore, again, the addition of a neuroleptic as it has an anxiolytic property would be justified.

The co-occurrence of anxiety and depression is particularly interesting from the standpoint of our analysis.

In their original article treating resistant major depression with olanzapine and fluoxetine the authors (Shelton) did not find a statistically significant improvement in depression with the Hamilton rating scale for depression, but they did find it with the Montgomery-Asberg depression rating scale (Shelton, C. R., et al. 2001 (a,)). Nevertheless, the author had find their finding, the improvement of depression, clinically significant. (Written communication from Shelton.)

In our explanation, - what might have gone unrecognized by these authors (and others in the process of replicating the study) – is, that there is a specific, significant difference between these two psychological rating scales. Namely, the Montgomery-Asberg depression rating scale puts a relatively higher emphasis on anxiety (1 in 10), while the Hamilton rating scale for depression has about the ratio of rating *psychic anxiety* 1 in 21. [Somatic symptoms/anxiety are measured separately.]

In addition, the Montgomery-Asberg depression rating scale allows a 0 to 6 measurement of the inner tension, potentially allowing more emphasis in the statistical analysis. In comparison, the Hamilton depression rating scale there is a 0-2, 0-3, and for anxiety 0-4 scoring. (For replicative studies, it is important of not to use a “simplified” Hamilton rating scale, where there is only a checkmark for the



depressive symptoms, not allowing any severity rating: [(See references for the scales: (Stajatovic, M. et al. (eds): 1999.)). That would make the Hamilton scale even more 'insensitive' to changes in anxiety. Never the less, what the authors (Shelton) might have actually measured (in coming up with a statistical difference in one scale, but not the other), was the relative improvement in anxiety. It is known that antipsychotics reduce anxiety. [Although this group of medications had been named "major tranquilizers" early on, it was because of their strange quietness or blandness (ataraxia) that the patients were displayed. (Van Kammen, D.P. 1995).] Undoubtedly, other factors might also play a role in why the combination of antidepressant with atypical antipsychotic medication results in an improvement in the treatment-resistant depression. We have already reviewed above some of the key factors that in our interpretation can contribute to the improvement of depression by adding an atypical neuroleptic, or a "dopamine system stabilizer".

In finding a rational, that why would the addition of a neuroleptic result in an almost immediate positive response in depression; we have to also rely on a psychological explanation. In short an immediate improvement in any of the patient's symptom would be a direct reinforcement that change is possible, and that would change the patient's expectation. Depressed patients, in general, have a low motivation, a decreased energy and interest, and an expectation that 'why bother', nothing is going to change, nothing is going to help. They have a helplessness and hopelessness. In fact these symptoms are characteristic of depression (and also a significant risk factor for suicide) [for helplessness being an increased risk for suicide see reference : A study by Fawcet (cit#16 in Forster P., 1994.)). Unfortunately, this is why many depressed people don't seek treatment. It's ironic, that when they come for an evaluation to their doctor, this negative expectation is just being reinforced. They cannot get an immediate relief, the evaluating doctor is asking a lot of questions about painful or negative aspects of their lives, (at times it seems to them that he/she is just dwelling on their problems). At the end of the first visit they are told that the antidepressant cannot help for several weeks. As a result the negative expectation is reinforced, and due to their hopelessness, they may discontinue taking their medication. (see also Yapko tape). In fact nonadherence to the prescribed medication can account for as many as 20% of the cases considered to be treatment-resistant. (Thase, M.: 2002 (b), references >Cit.#11.) About 24% of patients do not inform their physicians that they stopped taking antidepressants. (Demyttenaere, K. et al. 2001). Other publication reports that in primary care, more than one third of patients fail to refill their initial (antidepressant) prescription, and nearly half discontinue it within three months. (Pincus, H.A., et al. 2001.).

Therefore addressing and relieving the anxiety - which is present as a comorbid disorder in 56.8% of patients with known non-bipolar, major depressive disorder (Zimmerman, 2002) - would result in a drastic change in the patients' expectation. Since a positive change had occurred (a relieve in their anxiety, an improvement in their overall feelings), they would show more hope. Therefore, by pharmacologically addressing one symptom, improvement in other - related symptoms, and - in general - in the depression as whole, can be expected. That would explain the "immediate" improvement from the psychological point of view.

- Sleep disturbances (insomnia) is one of the depressive symptoms often present. So, addressing this problem early on would result (similarly) in improved compliance and in a more immediate improvement in the overall depressive symptoms as well. (Temporarily adding a sleeping pill - like zolpidem (Ambien), till the depressive symptoms, and with them, the complaint of insomnia would lift - can therefore have a more beneficial effect then what we realize, i.e. the improvement of sleep per se.)

It is important to note, that neuroleptics, in particular atypicals may improve sleep. (Salin-Pascual, R.J. et al. 1999.) That may again point to a benefit of the combination use of these medications with the antidepressants. (See also Eli Lilly patent# WO 99/61027 SSRI-antipsychotic combination use for adverse events associated [with SSRI administration] with the treatment of major depression, partial, or treatment resistant depression.)

- The more symptoms we address and correct “right away”, the better the chances of patient satisfaction and global improvement.

While I was in training, I have heard stories of the “miracle” effect of using stimulants as antidepressant in some medically ill/elderly patients. (Kamholz, B.A., et al. 1996). (See also reference for stimulant use in medically ill/elderly: Satel, S.L. et al 1988; also referenced in: Willner, P. 1997,) I have never put it in this context up till now, but a similar explanation may play a role here that by improving the patients’ energy we see a quicker response then with other antidepressants. With the global improvement, the patients’ expectation changes too, and hopelessness gets less pronounced, or goes away.

(However in defense of biological explanations, we have to note also the following: High placebo response plays a role in the treatment of depression (mean placebo response rate for major depressive disorder is about 30-40% with some studies reporting rates of 70% [Schatzberg A.F, et al 2000,]. Some also suggested with studies supporting that trend, that patients with more severe depression respond well to antidepressants whereas those mildly ill respond equally well to antidepressants and placebo. (Khan, A., et al. 2002, [see also Rush, A.J., 2000, Thase, M.E. 2002 a, 2002 c, and Kirsch, I. 2000, on if the drug and placebo effects are additive.); However, it is unlikely that placebo response would be the only explanation here. First, here the (adjunct) medication is chosen specifically to target pharmacologically a specific symptom (the anxiety, cognitive distortions “overlapping” with psychosis; low energy or sleep disturbance respectively), so it is not a “placebo”. Second, as we can see in the case report with the risperidone-SSRI combination for treatment-resistant depression (O’Connor, M., et al 1998) – at least in one case – it was reported that the patient did relapse despite the resolution of sleep problem (and despite the additional adjunctive use of a benzodiazepine as an anxiolytic); and it did not gave the same result in the improvement of depression as the added atypical antipsychotic did. So psychological explanation on the role of changing expectations is extremely important, but it is not the full answer.)

- We have mentioned above, that the atypical antipsychotic medications (at least in psychotic patients) show beneficial effect on the “negative symptoms” (Purdon, S.E. et al. 2001, Berman, I., et al 1999, Keefe, R.S.E., et al. 1999,). Within the “negative symptoms” the following terms are included: *affect blunting* which may correlate to such symptoms in depression as decreased interest, concentration, and psychomotor retardation. The term *anergia* correlates with the symptom of decreased energy. *Alogia* if due to depression may be because of decreased interest, psychomotor retardation, or decreased energy. *Social withdrawal* may occur for many reasons, but decreased interest, concentration, psychomotor retardation, guilt, and hopelessness (which are all symptoms of depression) can also play a role. The above is another reason of why the atypical neuroleptics could provide a benefit in the treatment of depression – as adjunct to the antidepressants.

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| PTO page 17, 0177 till page 18 end of 0178; (=my copy with font size 14 page 29 5 <sup>th</sup> paragraph till page 30 end of 1 <sup>st</sup> paragraph.): |
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Obviously when both psychosis and depression are present like in schizoaffective disorders, psychotic depression, or even at times in bipolar disorder, both groups of medication are indicated and used, targeting the depressive or psychotic symptoms respectively. (About 2/3<sup>rd</sup> of patients with bipolar (manic-depressive) disorder are having a history of at least one psychotic symptom. Bipolar patients who are psychotic during one episode of affective illness are highly likely to be psychotic during subsequent episodes. [Tsai, SY. M., et al. 2002.]). Antipsychotic medications also showed a value during the manic phase of the bipolar disorder. (See Miller, D. S. et al, 2001, Yatham, L.N. 2002, Sajatovic, M. et al. 2001.).

It has been also shown, that about 15% of major depressive disorders, usually those with melancholic features, develop into delusional (psychotic) depressions. (Akiskal, H.S. page1137, 1995).

PTO page 19, 0185 till page 20 line 2; (=my copy with font size 14 page 31 4<sup>th</sup> paragraph lines 1-3.)

In reviewing the recent paper (O'Connor, M. 1998) about the use of risperidone for treatment-resistant depression, it is notable that all of their patients had shown a comorbid anxiety.

PTO page 49, 0290; (=my copy with font size 14 page 61 2<sup>nd</sup> paragraph.):

For the different type of antidepressant actions see Thase (2000).

PTO page 38 0248 - till page 46 0277; (=my copy with font size 14 page 49 3<sup>rd</sup> paragraph till end of page 57.):

As per the phone interview with the PTO grammatical changes were allowed – we have clearly marked that by strikethrough and [in marked squared parenthesis – bolded - the added correction]. Additionally we have drawn attention to those changes here in the box where note on what page number the pasting came from. These are: ~~to~~ **[that we]**; go**[o]**d; **[how]**. For “(See text later and Appendix B and C **[of the provisional]**).” the **[of the provisional]** was added for clarity –as when we wrote it was in the provisional.

The interest in psychopharmacology research is also shifting. Instead of searching for medications with high affinity for D2 receptor, or agents that strongly binds to dopamine receptor, researchers are reevaluating their strategies. Agents can be both agonists and antagonists, or transiently binding to dopamine receptors, having mild effect similar to dopamine but less intense. The newest generation of atypical antipsychotics better named as “dopamine system stabilizers” are exemplified with the prototype of aripiprazole. (Krammer, T.A.M., 2002). It was shown that the single most powerful predictor of atypicality is fast dissociation from the D2 receptor. (Kapur, S., et al 2001). (See also for additional reference Stahl, S.M., 2001 a, 20001 b.).

Therefore, quetiapine, with it's fast dissociation from the dopamine receptor - relative to risperidone and olanzapine - may be reclassified in the future as a “dopamine system stabilizer” from it's current group of “atypical antipsychotics”. The above may give a better insight in looking at the role of dopamine in the treatment of depression.

We should also keep in mind that the role of dopamine may be specific to a particular brain area. In addition, the different subtypes of receptors mediate different actions, and these are further

affected by other neuromodulators. The end result is complex. That may also suggest to look for a molecular/biological solution elsewhere. We know that dopamine (DA) plays an important role in neuronal plasticity. (Spitzer, M. 1999). In looking the global picture, that is the role of neuronal plasticity in depression, the psychological and biological explanations blend together.

Although some may use the terms synaptic plasticity or neuroplasticity as synonymous, it may be better to separate the two phenomena. Synaptic plasticity as it relates to depression (and learning), is primarily referring to changes in the cellular, synaptic and molecular levels, with the focus on glutamate neurotransmission and NMDA receptors. One of the primary interests is on the volume loss of the hippocampus, with possible neuron loss during depression. It had been questioned if stress and elevated glucocorticoid levels (through oxygen radicals and “programmed cell death”) may cause hippocampal neuron loss associated with subtypes of chronic depression. (Lee, A.L. et al, 2002; Duman, R.S. et al. 1999,). There is evidence that stress will cause a regression of dendritic process in hippocampal neurons producing loss of neuronal volume, this however, has been shown to be reversible with the cessation of stress. (Lee, A.L. et al, 2002,). There had been an expectation that pharmacological inhibition of NMDA receptors would be protective against insults (and “programmed cell death”) (Lee, A.L. et al, 2002,), and that NMDA receptor antagonists act as antidepressants in certain animal models of depression. (Willner, P., 1997,). In frontal cortices of human suicide victims the alterations of NMDA subtype of glutamate receptor had been shown, (Nowak, G., et al. 1995, also referenced in: Heresco-Levy, U., et al 1998, and Krystal, J.H. et al. 1999,). It had been hypothesized that a final common pathway of antidepressant action may be associated with the NMDA receptor complex, as antidepressants may induce adaptive changes in the glycine (GLY) regulatory sites of the NMDA receptor. Antidepressants from every class produced a 2-4 fold reduction in the GLY to inhibit 5,7-DCKA binding to the NMDA receptor-associated GLY sites. (referenced in Heresco-Levy, U., et al 1998,). An antibiotic that had been used to treat tuberculosis, DCS (Seromycine) with a partial agonist character at the GLY site and with an NMDA antagonist-like effect (or mixed agonist/antagonist effect) had been shown to display prompt antidepressant effects (before the X-ray changes), while GLY too had shown an antidepressant effect (reducing negative schizophrenic symptoms). (Heresco-Levy, U., et al 1998,). Others also noted that there had been evidence demonstrating that mood stabilizers and antidepressants exert effects on signaling pathways which regulate synaptic plasticity and cell survival, (Manji/editorial, 2002,).

Unfortunately, there are also conflicting reports that makes the role of NMDA receptor difficult to understand. How can one explain the fact that a competitive NMDA receptor antagonist, a non-competitive NMDA antagonist, and a partial agonist all have shown efficacy in animal models of depression? (Belsham, B. 2001,). In addition the NMDA receptor antagonist (CPP) impairs learning and memory, and the same receptor complex is thought also to be involved in a variety of other psychiatric illnesses. (Shapiro, M., 2001,).

However, it is of particular interest to us, that the glutamate transmission (in patients with schizophrenia) is affected by atypical antipsychotics. (Evins, A.E. et al 1997, as referenced in Scheepers, F.E. et al. 2002,). In contrast to this above study, in cerebrospinal fluid (CSF) no significant change in glutamate concentrations was found after treatment with olanzapine (again in patients with schizophrenia). The authors also note that it is possible that the brain glutamate concentrations are not reflected in CSF. (Scheepers, F.E. et al. 2002,).

The synaptic plasticity model of depression also overlaps with the theory on the failure of neurogenesis (lack of brain cell growth) linked to depression. (Vogel, G. 2000). Neuroimaging techniques show smaller hippocampi in depressed patients, and antidepressant drugs and electroconvulsive therapy (in animals) show significantly more newly divided cells in the hippocampus. This is an addition to the recent discovery that had shown that the brain keeps producing new neurons into adulthood. (Vogel, G. 2000, Duman, R.S., et al 2000,).

Looking beyond the changes in the hippocampus and receptor level in depressed patients, it would be worthwhile to separate the term synaptic plasticity from neuronal plasticity.

Neuronal plasticity, the capacity of the brain to respond to changes (Spitzer, M. 1999,) had been extensively studied in some other conditions where the cortical representations of somatic perceptions can be mapped. (As the brain has no sense of pain, neurosurgeons could operate on patients while they were conscious [in local anesthesia or “woken up” after their skulls were opened] for example to remove a tumor, but to preserve brain areas that are essential to speech, vision or movement. During such operations it was discovered that part of the cortex that is responsible for processing touch sensations and is representing the different areas of the body, has a map-like structure, called “homunculus” in the cortex. Not only touching, but all senses are represented in topographical cortical maps. [See also: Spitzer, M. 1999,]).

What is the most intriguing is, that these cortical maps or cortical representations are not fixed, but have the ability to change if the input is changing (i.e. to show neuroplasticity). In a congenital malformation called syndactyly, the fingers are attached to each other (like in a fetal webbing). After the fingers are surgically separated, the borders between their cortical representations emerge in one week. (Mogliner et al. as referenced in Spitzer, M. 1999,). The opposite was also shown in animal experiments sawing the fingers together. Changes in cortical representation do follow this procedure.

In a different experiment (seen at PBS), a human volunteer was blindfolded for about two weeks, and it was found through a non- or minimally invasive procedure, that other brain areas started to “took over” the now unused visual cortex, and the cortical representations of the fingertips (touching) had increased.

It is interesting to compare that while it takes weeks for the antidepressants to start working, it also took week(s) to see neuroplasticity changes in the above experiments.

For a more complex adaptation neuronal changes may take even a year (e.g. cochlea implant). (Spitzer, M. 1999,).

The above experiments are looking beyond the changes in the hippocampus (and are not constricted to the receptor level). Different emotions, or the changes in depressive disorders are not limited to the hippocampus, and other brain areas are also involved.

Beyond the cellular changes in the hippocampus, and beyond the explanation of changes at intracellular level, the only strong support for the neuronal plasticity of depression, that we have seen was the argument that the therapeutic action of antidepressants requires weeks, even though these medications block the reuptake or metabolism of norepinephrine (NE) and serotonin (5-HT) much more rapidly. The conclusion was that therefore the treatment of depression involves adaptation or plasticity of neural systems. (Duman, R.S. et al, 1999,).

Yet it would be interesting to see a synthesis of clinical findings, supporting the neuronal plasticity model of depression from the clinical standpoint. Below we will present our viewpoint

that brings the psychological and biological explanations together, and provides further understanding of depression. [These were never presented in this context before].

First we'd like to start with the "domino metaphor" (or "practice makes a master" metaphor). Although traditionally it was believed, that if stroke victims did not regain the function of their arm within a few months, then it was little hope for recovery, we know it now that this is no longer true. Supported by clinical data and not just animal experiments, we know that persons with stroke "learn" of not to try using their paralyzed arms or legs, and as times goes on this becomes an increasingly powerful conditioned response. However, by placing a restraint (a large stuffed mitt) on the patient's functioning arm, he/she is forced to overcome the tendency of not using his/her weaker arm. With physical therapy they are coached 6 hours a day to practice and improve the movements of their weak extremity. They are given tasks like turning dominos over (and cheered for their success). With practice and repetition comes a dramatic change within a few weeks. This phenomenon had been explained as a result of "an increased recruitment of neurons surrounding the area of the primary damage caused by a stroke". The neurons that haven't been killed by the stroke, but are in the vicinity of the damage are sending out connections with other neurons. (Restak, R.M., 2001 and corresponding PBS video). This is the neuronal plasticity that we have also seen in other examples above. In principles we see a similar phenomenon when children's good eye is covered to force the weaker eye to "learn to see". With practice we are relying on neuronal plasticity in a therapeutic way.

Now, if this true on other areas, why wouldn't it be true for depression, or for the treatment of depression? In fact we have unpublicized data available to support that most likely the same is true for depression. Depressed people tend to focus on the negatives, and tend to ignore seeing the positives. Cognitive therapy teaches us to do similar repetitions, that is, to catch ourselves ~~to~~ [that we] have (negative) automatic thoughts, and make necessary corrections by doing an analysis of the facts on both the negative and the positive side. This is the practice that is similar to the "repetitions of the movements" seen in stroke victims above. We just do not have a go[old] visible "mitt" that would force us doing this practice. However medications do help exactly in that direction: We have mentioned above, that the problem in depression is rumination, the repetition and overt focus on the negatives, with cognitive distortion. Actually SSRIs used for treating depression are also working to reduce OCD symptoms, "the rumination". We suggested above that neuroleptics may also be helpful in many ways, and are expected to help decreasing cognitive distortions, that are so characteristic of and contribute to the depression.

However, let see [how] some experiments from decades ago can be applied in this context, so that with our current knowledge they would clinically support the neuroplasticity model of depression.

One of the experiments, (Haney, C., et al. 1973, also referenced in Yardley, K.M. (1982 b), and see also as related reference: Yardley, K.M. (1982 a),), although was not designed to do anything with depression, but has a great relevance to it, as it shows the importance of how detrimental can a 'negative practice' be even in "as-if" (or role play) situations. In a Stanford experiment they recruited normal healthy volunteers who agreed to take part of a "prison simulation experiment" for up to two weeks. They randomly assigned them to be either "prisoners" or "guards". Unlike the guards, who had some minimal warm-up to the as-if event, 'the prisoners were covertly inducted, without their conscious cooperation. For the sake of "realism", they were arrested in the early morning, on false burglary charges, by actual members of the city police who were cooperating with the experimenters. The prisoners were then subjected to police interrogation and taken blindfolded to the simulated prison.' (Haney, C., et al.

1973, also referenced in Yardley, K.M. (1982 b),). The “prisoners” were further subjected to humiliating and frustrating experiences (and their queries to the police if this had to do anything with the experiment were ignored). After a week the experiment needed to be prematurely terminated, “due to the ensuing emotional disturbances amongst the participants, particularly amongst the prisoners”. ( Yardley, K.M. (1982 b),). The “prisoners” were feeling powerless, loss of control to the point of oppression, frustration, ‘emasculatation’, anonymity, and arbitrary rule. The later in this case is really resulted in “learned helplessness” that we know as an important causative factor in the development of depression. While this experiment from the early 1970’s looks cruel, and we can all hope that this kind of “experiments” can no longer be done today, they show something, that artificially practicing and focusing on the negatives, or be forced to focus on the negatives even in an “as-if” experiment would result in an unwanted emotional disturbance. This is exactly the opposite of what we therapists and health care professionals want to achieve, and an example that “neuroplasticity” works both ways. In a commentary on the above ‘experiment’ Yardley notes that the outcome would have been different if the participants would have been brought out of the as-if situation every few hours or so to remind them of the as-if framing. (Yardley, K.M. (1982 b),). That means of shifting the balance between the negatives and positives. This is what depression therapy is all about when we give the patients the tools of doing this.

In another experiment unemployed actors were recruited for a depression study. They were paid volunteers, and were asked to act and think as-if depressed, to walk slowly with a bended posture, and think that they are no good, etc. In two weeks they have shown biochemical and other signs of depression, and the actors reported that they had difficulty snapping out of the depression after the experiment was over.

All of the above supports not only the “clinical neuroplasticity model of depression”, but also the importance of practice to overcome depression. In this context this is very similar to the therapy of the stroke victims mentioned above. This “domino metaphor” (or “practice makes a master” metaphor) can also be used clinically to motivate and educate patients about depression, and depression treatment.

The above – the neuronal plasticity model - can also give an insight to the course of depression, and to the ‘natural’ tendency to relapse, of why is that so easy to relapse, if one stops the medication(s), or stops the ‘positive “domino” practice’. It was shown, that practicing cognitive therapy can be protective of the depressive relapse, and this is supportive of this view. It was also shown that the combination of antidepressant and cognitive therapy is superior to either treatment alone. [see Thase].

One of the reasons for why the neuroplasticity model of depression is still lagging behind the other observations on the brain’s power to adapt is that our technology did not allow us to “map” the cortical representations and changes that occur with the depression. Our brain imaging techniques are improving (George, M.S. 1994, Ketter, T.A., et al. 1994, George, M.S., et al. 1994, Rubin, E., et al. 1994.), but there is another way to assess and “map” changes in the brain. The cortical representation of one’s “inner world” may be also reflected by one’s vocabulary. It had been shown, that in children, at an early age, words referring to the imaginary world (like fairies, dragons, etc.) shows a relative high ratio to reality based words in comparison to adulthood. (Deme, L. personal communication, Deme, L. 1975,). This “mapping” of children’s vocabulary is in turn is also correlates with the finding that children has a greater involvement in fantasy, and have a higher hypnotic susceptibility. (Migaly, P. 1991). Although it is not the same, but assessing patients depression (or feelings) with a psychological test, that we propose for a more accurate assessment of depression, can serve as a “mapping”

tool. (See text later and Appendix B and C [of the provisional]). With an analogy it is like the vocabulary in the RAM or the hardware of speech recognition software. The words used (thought/ruminated) more often are stored upfront (RAM), but other words are still recognized that are stored in the hardware. So mapping of the neuroplasticity changes occurring during or in the recovery of depression is also possible with a psychological tool relying on the vocabulary. (One has to be careful though to balance the testing with counseling and of not to alter with too frequent testing the “positive – domino – practice” encountered in therapy, or by the positive effect of the medications).

In helping someone to come out of depression (and one’s inner world of focusing on the negatives), it had been shown that physical exercise has a value, and an antidepressant effect. (Russo-Neustadt, A., et al 1999, Blumenthal, J.A., et al 1999,). We also know, that in chronic pain, that frequently also overlaps with depression, physical activity has a beneficial effect. Moreover, physical exercise was also shown to be of value in connection with learning and neuronal plasticity. These similarities are intriguing.

It had been questioned before that if for the depressed patients everything would go exactly their way for a few solid weeks, without disappointments, rejections or criticism while everybody would love them, would their depression go away? (O’Connor, R. 2001 p23). Well, it depends. These circumstances could definitely make everybody’s life easier, but recovery to a large extent depends on “the domino metaphor” practice above. (However, the “optimal circumstances” raised in the above question are so important that in our upcoming book we are paying attention to on how to achieve the most and get a harmony, a ‘full life’ not just recovery from depression.) In fact the closing remarks in a book where there is a lot of discussion about neuronal plasticity emphasises that we all should “watch our mental diet”. (Spitzer, M. 1999,). In this the author means that we should watch the input we receive (e.g. through violent movies, discouraging news from within the society).

In summary for this section in looking the global picture, that is the role of neuronal plasticity in depression, the psychological and biological explanations indeed do blend together.

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| PTO page 51 0297 - till end of 0298; (=my copy with font size 14 page 62 2 <sup>nd</sup> paragraph.): |
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A new research of data (although pertaining to a different group of disorders, the bipolar disorder, and bipolar depression) brings up the issue of “neuroprotection” from the standpoint of the neuroplasticity, and “programmed cell death” that is associated with bipolar disorder, and bipolar depression. (Lee, A.L. et al, 2002, Manji/editorial, 2002, Chuang, D-M., et al. 2002, Bown, C.D. et al. 2002, Li, X. et al, 2002,) (See also Spitzer, M., 1999, Grigsby, J. et al. 2000, Fazeli, M.S. et al 1996, Restak, R. 2001, Duman, R.S. et al. 1999, ref. for neuroplasticity).

If this data also can be replicated for major depression, there would be an additional benefit at the molecular and cellular level for the combined use of mood stabilizers. [It would be also interesting to see if antidepressants and neuroleptics show this “neuroprotective effect”. Some of the atypical neuroleptics had also shown a “mood stabilizing” effect in mania. However, not all mood stabilizers had shown a “neuroprotective effect”.] We are getting now mood stabilizers that have substantially less side effects. For now the combined use of a mood stabilizer together with a (newer) antidepressant/or SSRI with or without the added neuroleptic should be considered very carefully only for selected patients when used in non-treatment resistant cases until we get more data, or mood stabilizers with



safer side effect profile. In other words their risk/benefit ratio has to be measured before use. [We mentioned for example suicidality or impulsiveness.] However, these medications – in combination – should be considered to be given right away, to reduce the risk of suicide.

PTO page 52 0307; (=my copy with font size 14 page 62 2<sup>nd</sup> paragraph.):

The invention also provides a method where other medications traditionally used for as adjunct medications reserved for treatment-resistant depression, can be considered to be given right away in the treatment of major depressive disorder, other depressive disorders, and/ or in disorders high risk for suicide to achieve a reduction of suicide. (See Nelson e.g. for reviewing agents used for augmentation strategies for treatment-resistant depression).

PTO page 57-58 0333; (=my copy with font size 14 page 68 5<sup>th</sup> paragraph till page 69 lines 1-2.):

The above claims should not be limited by the patient taking other medications as well, or by using other augmentation strategy by e.g. by combining more than one antidepressants, or by using other strategy like of pushing up the dose of the antidepressant aggressively. This later is usually not followed, unless there is a comorbid disorder (like an eating disorder) where usually higher dose of the antidepressant is required for adequate treatment. Alternatively combining antidepressants and 5-HT agent (like pindolol), - with or without antipsychotics should also not limit the above claims. Similarly, addressing sleeping problems right away is important in achieving a rapid response/ increased compliance, and should get a weighted emphasis. However, its benefit seems not to be the same as with the psychotropic combination we had been suggesting above.

From claim 6 of the provisional: PTO page 77. (=my copy with font size 14 page 19 [from claim 6], till page 20.):

an antipsychotic medication or a “dopamine system stabilizer” alone and/or in combination with an antidepressant can also be used in other circumstances where depressive symptoms and/or anxiety/irritation could be the predominant symptom in the patients, but the patients/clients do not need to meet diagnostic criteria for major depressive disorder. In this case the antipsychotic medication or the “dopamine system stabilizer” and/or the combination use do not need to be for the reduction of suicide, but for the reduction of anxiety/irritation, and/or the depressive symptoms, and/or compulsivity and/or possibly the reduction of cognitive distortions as well.

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**SUMMARY AND CONCLUSIONS**

In view of the foregoing, it is respectfully submitted that the amended claims are supported by an enabling disclosure and are patentable over the applied art. As a result, it is respectfully submitted that Claims 1-38, 41-43 and 48-118 and new Claims 119-130 are in proper form for issuance of a Notice of Allowance and such action is respectfully requested at an early date.

**If for any reason you would feel that any of the claims as amended would not be allowed, please schedule a meeting with the Applicant.**

The Applicant's cell phone number (voicemail identifying him) is:

(724)840-0464

**Please note, that the Applicant have lost his attorney representation, and is relying on your guidance.**



Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Peter Migaly'.

Peter Migaly, M.D.